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PATENT & TRADEMARK OFFICE
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MERCK & CO., INC.

By Nancy J. Lynch Date 3/20/2009

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Nigel J. Liverton et al.	
Serial No.:	10/559,153	Case No.: 21414P
US Nat'l Filing Date:	December 5, 2005	
Int'l Appl'n No.:	PCT/US2004/017175	
Int'l Filing Date:	28 May 2004	
For:	3-FLUORO-PIPERIDINES AS NMDA/NR2B ANTAGONISTS	

Group Art
Unit:
1625

Examiner:
Nizal S.
Chandrukumar

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JOSEPH J. LYNCH UNDER 37 C.F.R. § 1.132

I, Joseph J. Lynch, hereby declare as follows:

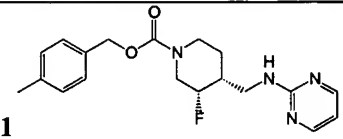
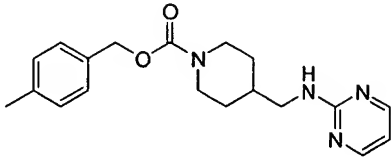
1. I am a citizen of the United States, and am over 21 years of age. I have been employed by Merck & Co., Inc., since 1988 as a pharmacologist. I am presently Senior Director in the Integrative Systems Neuroscience Department of Merck. A copy of my curriculum vitae is attached at Exhibit A.

2. As part of my job responsibilities at Merck, during the period of from about 2001 to 2004, I was a member of Merck's NMDA/NR2B development team. One of my roles on the team was to provide biological testing of NMDA/NR2B ligands developed by Merck's medicinal chemists. The testing was done at my direction and under my supervision, in my laboratory at Merck's West Point, Pennsylvania research facility. The testing was done to evaluate the ligands as potential drug candidates. I tested compounds disclosed and claimed in both International Application WO 02/068409 and International Application WO 2004/108705. I understand that the instant U.S. patent application for which I am making this Declaration is the U.S. national phase of the application published as WO 2004/108705.

3. The testing performed in my laboratory, and under my supervision, included *in vivo* occupancy testing of the NMDA/NR2B rat receptor.

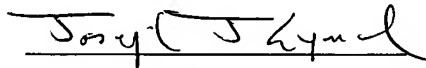
4. Rat Receptor Occupancy Testing. The ability of compounds to inhibit the *in vivo* occupancy of the selective NR2B ligand [3H]- N-(3,5-dichlorobenzyl)-4-(fluoromethoxy)benzenecarboximidamide in the rat frontal cortex was assessed using an adaptation of the method for assessing inhibition of [3H]-MK-801 binding to NMDA receptors in mouse brain described previously. Male Sprague Dawley rats (95-125 grams; Taconic) that had been dosed intravenously with test compound were placed in a restrainer and administered 200 μ Ci/kg IV [3H]- N-(3,5-dichlorobenzyl)-4-(fluoromethoxy)benzenecarboximidamide (specific activity = 18 Ci/mmol) into a lateral tail vein and euthanized via CO₂ inhalation at 7.5 min after injection of tracer. A 100-150 mg slice of frontal cortex was quickly removed, weighed and homogenized (PT3100 Polytron) in 39 volumes cold HEPES buffer (10 mM). Homogenate (500 μ L) was immediately filtered through 25mm Pall A/E filters (pre-soaked in 0.2% polyethyleminine) and washed [5 x 5 ml of cold HEPES buffer (5 mM KCl, 150 mM NaCl, 10 mM HEPES)]. The filters and duplicate 500 microliter aliquots of unfiltered homogenate were placed in scintillation vials, Ultima Gold scintillation fluid (10 mL added), samples equilibrated for 4 hours and counted in a Packard Tri-Carb 2900 TR Liquid Scintillation Analyzer. ED₅₀ values of representative compounds from the instant application and from WO 02/068409, are provided below in Table 2.

Table 2

Application Serial No. 10/559,153		WO 02/068409	
Example	ED ₅₀	Example	ED ₅₀
<p>1</p> 	0.2	<p>17</p> 	1.4

10. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or

imprisonment or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the instant application or any patent issued thereon.

A handwritten signature in dark ink, appearing to read "Joseph J. Lynch", written over a horizontal line.

Joseph J. Lynch

Dated: 17 March 2009

CURRICULUM VITAE

I. PERSONAL

A. Name: Joseph John Lynch Jr.
B. Home Address: 892 Quinn Lane
Lansdale, PA 19446
C. Home Telephone Number: 610-584-6076

II. EDUCATION

<u>School</u>	<u>Date</u>	<u>Major</u>	<u>Degree</u>
Loyola College Baltimore, Maryland	1974-78	Biology	B.S. Summa Cum Laude
Ohio State University Columbus, Ohio	1978-82	Pharmacology	Ph.D.

III. MERCK EMPLOYMENT HISTORY

<u>Title</u>	<u>From - To</u>
Senior Director, Pharmacology, Integrative Systems Neuroscience	2000 – present
Director, <u>In Vivo</u> Pharmacology	1993 - 2000
Associate Director, Pharmacology	1990 - 1993
Senior Research Pharmacologist	1988 - 1990

IV. NON-MERCK EMPLOYMENT HISTORY

See V. Below

V. ACADEMIC EXPERIENCE

<u>Title</u>	<u>From - To</u>
Assistant Research Scientist, University of Michigan	1986-1988
Research Investigator, University of Michigan	1985-1986
Postdoctoral Fellow, University of Michigan	1983-1985

**VI. TRAINING BEYOND FORMAL EDUCATION
(RELEVANT TO PROFESSIONAL ADVANCEMENT)**

Merck Management Action Process - Substance Abuse Policy Training (1992)
Merck Management Training (1993)
Merck Leadership Development Program (1996)
Drug Metabolism Short Course (1998)
Merck Biology/Medicinal Chemistry Course (1999)
Merck Executive Leadership Development Program (2000)
Animal Handling Area Screening Skills Workshop (2001)

VII. SOCIETY MEMBERSHIPS

American Society for Pharmacology and Experimental Therapeutics
Fellow, Council on Basic Cardiovascular Sciences of the American Heart Association
International Society for Heart Research, American Section
Cardiac Electrophysiologic Society

VIII. ACADEMIC AND PROFESSIONAL HONORS

1974-78	Loyola College Presidential and Maryland State Senatorial Scholarships
1978	Loyola College Carroll Biology Medal
1978	B.S. Degree, Summa Cum Laude
1979, 80, 81	American Foundation for Pharmaceutical Education (AFPE) Fellowships
1980, 81	Eli Lilly - AFPE Pharmacology/Toxicology Fellowships
1983, 84	American Heart Association of Michigan Postdoctoral Fellowships
1985-1988	NIH New Investigator Research Award
1995-Present	Editorial Advisory Board, Journal of Pharmacology and Experimental Therapeutics
2001	Fellow of the American Heart Association Council on Basic Cardiovascular Sciences and Fellow of the American Heart Association (F.A.H.A.)
2001-Present	Editorial Board, Journal of Cardiovascular Pharmacology
2006	The Ohio State University College of Pharmacy Jack L. Beal Postbaccalaureate Alumni Award

IX. PUBLICATIONS AND PATENTS

Full Manuscripts (Peer Reviewed):

1. Lynch, J.J., Rahwan, R.G. and Witiak, D.T.: Effects of 2-substituted 3-dimethylamino- 5,6-methylenedioxyindenes on calcium-induced arrhythmias. *J. Cardiovasc. Pharmacol.* 3: 49-60, 1981.
2. Lynch, J.J., Rahwan, R.G. and Witiak, D.T.: Effects of tertiary and quaternary derivatives of aminomethylenedioxyindenes on the mechanical and electrical activity of isolated guinea pig atria. *Pharmacology* 25: 18-25, 1982.
3. Lynch, J.J. and Rahwan, R.G.: Absence of blocking effects on cardiac slow calcium channels by the intracellular calcium antagonist 2-n-propyl 3-dimethylamino-5,6-methylenedioxyindene. *Can. J. Physiol. Pharmacol.* 60: 841-849, 1982.
4. Lynch, J.J., Rahwan, R.G., Brumbaugh, R. and Witiak, D.T.: Effects of tertiary and quaternary derivatives of aminomethylenedioxyindenes on experimental arrhythmias. *Can. J. Physiol. Pharmacol.* 60: 1636-1642, 1982.
5. Lynch, J.J. and Rahwan, R.G.: Comparisons of the characteristics of the negative inotropic actions of dinitrophenol, rotenone, antimycin A and the intracellular calcium antagonist, propyl-methylenedioxyindene. *Gen. Pharmacol.* 14: 437-444, 1983.
6. Lynch, J.J., Rahwan, R.G., Witiak, D.T. and Cazer, F.D.: Intracellular localization of the calcium antagonist propyl-methylenedioxyindene in cardiac tissue. *Gen. Pharmacol.* 14: 571-578, 1983.
7. Patterson, E., Lynch, J.J. and Lucchesi, B.R.: Antiarrhythmic and antifibrillatory actions of the beta-adrenergic receptor antagonist d,l - sotalol. *J. Pharmacol. Exp. Therap.* 230: 519-526, 1984.
8. Patterson, E., Montgomery, D.G., Lynch, J.J. and Lucchesi, B.R.: Cardiac electrophysiologic actions of KB-944 (Fostedil), a new calcium antagonist, in the anesthetized dog. *J. Pharmacol. Exp. Therap.* 230: 632-640, 1984.
9. Lynch, J.J. and Lucchesi, B.R.: New antiarrhythmic agents: The pharmacology and clinical use of encainide. *Prac. Cardiol.* 10: 109-132, 1984.
10. Lynch, J.J., Wilber, D.J., Montgomery, D.G., Hsieh, T.M., Patterson, E. and Lucchesi, B.R.: Antiarrhythmic and antifibrillatory actions of the levo- and dextrorotatory isomers of sotalol. *J. Cardiovasc. Pharmacol.* 6: 1132-1141, 1984.

11. Wilber, D.J., Lynch, J.J., Montgomery, D.G. and Lucchesi, B.R.: Postinfarction sudden death: Significance of inducible ventricular tachycardia and infarct size in a conscious canine model. *Am. Heart J.* 109: 8-18, 1985; Abstracted in the Yearbook of Emergency Medicine, 1986.
12. Lynch, J.J., Rahwan, R.G. and Lucchesi, B.R.: Antifibrillatory actions of bepridil and butyl-MDI, two intracellular calcium antagonists. *Eur. J. Pharmacol.* 111: 9-16, 1985.
13. Lynch, J.J., Montgomery, D.G., Ventura, A. and Lucchesi, B.R.: Antiarrhythmic and electrophysiologic effects of bepridil in chronically infarcted conscious dogs. *J. Pharmacol. Exp. Therap.* 234: 72-80, 1985.
14. Lynch, J.J. and Lucchesi, B.R.: New antiarrhythmic agents: The pharmacology and clinical use of tocainide. *Prac. Cardiol* 11: 108-137, 1985.
15. Lynch, J.J., Coskey, L.A., Montgomery, D.G. and Lucchesi, B.R.: Prevention of ventricular fibrillation by dextrorotatory sotalol in a conscious canine model of sudden coronary death. *Am. Heart J.* 109: 949-958, 1985.
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17. Lynch, J.J., Montgomery, D.G., Ventura, A., Wilber, D.J. and Lucchesi, B.R.: Antiarrhythmic vs antifibrillatory activity of the basic diphenylhydantoin derivative 3- [3-(4-phenyl-1-piperidyl)propyl]-5-(4-methoxyphenyl)-5-phenylhydantoin hydrochloride. *Arzneimittel - Forsch/Drug Research* 36: 475-482, 1986.
18. Lynch, J.J., Montgomery, D.G. and Lucchesi, B.R.: Facilitation of lethal ventricular arrhythmias by therapeutic digoxin in conscious postinfarction dogs. *Am. Heart J.* 111: 883-890, 1986.
19. Lucchesi, B.R. and Lynch, J.J.: Preclinical assessment of antiarrhythmic drugs. *Federation Proceedings* 45: 2197-2205, 1986.
20. Lynch, J.J., DiCarlo, L.A., Montgomery, D.G. and Lucchesi, B.R.: Electrophysiologic effects of bepridil in normal and infarcted canine myocardium. *J. Cardiovasc. Pharmacol.* 8: 957-966, 1986.
21. Lynch, J.J., DiCarlo, L.A., Montgomery, D.G., Hassan, T. and Lucchesi, B.R.: Electrophysiologic effects of pirmenol in dogs with recent myocardial infarction. *Am. Heart J.* 112: 752-758, 1986.
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23. Lynch, J.J., Montgomery, D.G. and Lucchesi, B.R.: The effects of calcium entry blockade on the vulnerability of infarcted canine myocardium toward ventricular fibrillation. *J. Pharmacol. Exp. Therap.* 239: 340-345, 1986.
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26. Lynch, J.J., Montgomery, D.G., Nelson, S.D., Huante, D.M. and Lucchesi, B.R.: Lack of concordance between the antiarrhythmic and antifibrillatory actions of UM-424, a quaternary ammonium analogue of propranolol. *J. Cardiovasc. Pharmacol.* 9: 414-424, 1987.
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29. Wilber, D.J., Lynch, J.J., Montgomery, D.G. and Lucchesi, B.R.: Alpha adrenergic influences in canine ischemic arrhythmias: Effects of alpha-1 adrenoceptor blockade with prazosin. *J. Cardiovasc. Pharmacol.* 10: 96-106, 1987.
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Patents:

1. United States Patent 5,597,818. Methods of Treating Cardiac Arrhythmia. Issued January 28, 1997. Inventors: M.C. Sanguinetti, J.J. Salata, J.J. Lynch (Method of treatment of cardiac arrhythmia with selective I_{K_S} blockers).
2. United States Patent 5,776,930. Pharmaceutical Preparation. Issued July 7, 1998. Inventors: J.J. Lynch, J.J. Salata (Method of treatment of cardiac arrhythmia with combined use of beta-adrenoceptor blockers and selective I_{K_S} blockers).
3. United States Patent 5,935,945. Methods of Treating or Preventing Cardiac Arrhythmia. Issued August 10, 1999. Inventors: J.J. Lynch, R.J. Swanson, J.J. Salata, B. Fermini (Method of treatment of cardiac arrhythmia with $I_{K_{ur}}$ blocker phosphine oxide compounds).
4. United States Patent 5,969,017. Methods of Treating or Preventing Cardiac Arrhythmia. Issued August 10, 1999. Inventors: J.J. Lynch, R.J. Swanson, J.J. Salata, B. Fermini (Method of treatment of cardiac arrhythmia with use-dependent $I_{K_{ur}}$ blocker phosphine oxide compounds).

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